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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/475,470	06/07/95	SAMULSKI R	115132-4

18N2/0521

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EXAMINER	
NELSON, A	
ART UNIT	PAPER NUMBER
1809	14

DATE MAILED: 05/21/97

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No.	Applicant(s)
08/475,470	Richard J. Samulski, et al.
Examiner	**Group Art Unit**
Amy Nelson	1809

☒ Responsive to communication(s) filed on *Mar 5, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-45* is/are pending in the application.

Of the above, claim(s) *36-38 and 40-45* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-35 and 39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of Group I, claims 1-35 and 39, in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 36-38 and 40-45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 12.

2. The objection to the specification and rejection of claims 18, 32, 35 and 38 under 35 U.S.C. 112, first paragraph, in the Official action mailed September 3, 1996, have been withdrawn in view of applicant's arguments.

3. Rejection of claims 1-35 and 39 under 35 U.S.C. § 112, first paragraph, in the Official action mailed September 3, 1996, has been withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 112

4. Claims 1-35 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant claims a recombinant adeno-associated virus (AAV) vector which comprises a portion of the adeno-associated virus genome, a eukaryotic cis-acting regulatory sequence, and a eukaryotic nucleic acid sequence that encodes a therapeutic protein. Applicant also claims a multitude of different embodiments of the recombinant adeno-associated virus vector. The incorporation of the term "therapeutic" into the claims limits the claims to vectors that are enabled for *in vivo* uses.

Applicant teaches how to make a recombinant AAV vector that comprises hypersensitive site II (HS II) of the locus control region (LCR) of the globin gene cluster, the ^{A}gamma globin gene, and neomycin resistance gene (neo). Applicant teaches how to make said vector with HS IV, HS III, and HS II, in combination. Applicant also teaches how to make a recombinant AAV vector comprising the CMV promoter, β-galactosidase gene, and the mP1 RNA processing signals, as well as a vector comprising the RSV promoter, FACC gene and the SV40 polyadenylation signal. Applicant teaches that the recombinant vectors can be transduced into various cell lines in culture, resulting in expression of the introduced gene, as determined by RT-PCR. Applicant also teaches that transduction of lymphoblasts or of $CD34^{+}$ primary

hematopoietic cells from a FA(C) patient with the recombinant AAV vector comprising the FACC gene results in enhanced resistance to the clastogenic agent, mitomycin C (MMC). Finally, applicant teaches that transduction of $CD34^+$ primary hematopoietic cells from a patient with Hb SS disease with the recombinant AAV vector comprising HS IV, HS III and HS II operably linked to the ^{A}gamma globin gene results in an increase in the percentage of fetal Hb (HbF) in the transduced cells. Applicant does not teach how to use any of the claimed or disclosed recombinant AAV vectors therapeutically, *i.e.* how to treat a condition *in vivo*.

In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. The state of the art for gene therapy using recombinant viral vectors is highly unpredictable and hence significant guidance is required to practice the art without undue experimentation (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995). In particular, significant guidance is required relating to how to administer and target the vector or transduced cells to a patient, how to ensure adequate expression levels and sustained expression, how to achieve expression in a high enough percentage of the target cells and to ensure retention of the transduced phenotype in progeny cells, such that a desired therapeutic effect is achieved.

The instant invention is not enabled because the amount of guidance in the specification is not commensurate with the level of unpredictability in the art. Although applicant has demonstrated successful transduction of certain cell types with the disclosed recombinant AAV vectors *in vitro*, applicant has not taught how to use any of the recombinant vectors to treat a specific condition *in vivo*. Demonstration of successful expression of an introduced gene in cells in culture is far from demonstration of successful expression of the gene in cells *in vivo*, such that the transduced cells express the gene to a sufficient level, that enough cells are transduced and successfully taken up by the patient, and that the introduced gene is stably maintained in the target cells and transferred to their progeny cells so as to achieve a desired therapeutic effect. Specifically, applicant has not taught how to remedy or alleviate the symptoms of FACC, Hb SS disease, or any other condition in a patient. In the absence of guidance directed toward treatment of a condition, the invention as claimed is not enabled. When the *Wands* factors are weighed it is concluded that undue experimentation would be required to practice the invention, and therefore the invention is not enabled.

This rejection could be overcome by amendment of the claims to delete the term "therapeutic," however then applicant would need to overcome the art rejections (see below).

5. Rejection of claims 1-35 and 39 under 35 U.S.C. §112, second paragraph, in the Official action mailed September 3, 1996, has been withdrawn in view of applicant's amendments to the claims.

Effective Filing Date

6. As stated in the last Official action mailed September 3, 1996, there is no support in any of the parent applications for claims 33-35, directed to a recombinant AAV vector comprising a gene encoding FACC. Hence, for those claims, applicant is entitled only to the effective filing date of the instant application, namely June 7, 1995.

Applicant submits that this subject matter was disclosed in the application filed June 3, 1992, which is application Serial No. 07/893,513. Specifically, applicant points to page 9, lines 15-20 and page 18, lines 15-16 and lines 19-23 in the specification for support for methods of using rAAV vectors with cis-acting regulatory elements and the use of rAAV to treat blood-related disorders. The cited lines on page 9 of the specification are directed toward preparing helper free stocks of recombinant adeno-associated virus, and the cited lines on page 18 do not exist. Hence, examiner still maintains that there is no support for recombinant AAV vectors comprising a gene encoding FACC in any of the parent applications, and therefore claims 33-35 are considered to have an effective filing date of June 7, 1995, the date of the instantly filed application.

Claim Rejections - 35 USC § 102/103

7. Rejections of claims 1-26 and 33-35 under 35 U.S.C. §102 (b) and of claims 27-32 and 39 under 35 U.S.C. §103 (a), in the last Official action mailed September 3, 1996, has been

withdrawn in view of the institution of a new ground of rejection under 35 U.S.C. §112, first paragraph. However, applicant should note that amendment of the instant claims to delete the term "therapeutic" will result in the reinstitution of these rejections.

Applicant argues that the cited Walsh reference is not an enabling teaching of the present invention, that one skilled in the art could not, upon reading the cited Walsh reference, construct a recombinant adeno-associated virus vector comprising at leaast a portion of the adeno-associated virus genome, at least one eukaryotic based cis-acting regulatory sequence, and at least one eukaryotic based nucleic acid sequence that encodes a therapeutic protein. Examiner concedes that the Walsh reference does not teach how to make and use said construct, wherein the construct comprises a gene that encodes a therapeutic protein, because said construct reads on *in vivo* uses, and the reference does not enable *in vivo* uses. However, if applicant were to delete the term "therapeutic" from the claims, then the Walsh reference does indeed teach all of the essential components of the claimed recombinant AAV vectors and how they are to be assembled, given the knowledge regarding AAV vectors and the ordinary skill in the art at the time of the invention. Walsh recites a recombinant AAV vector comprising the globin gene operably linked to the LCR site II, and further comprising the neomycin resistance gene, and teaches that said vector can be stably tranfected into erythroleukemia K562 cells.

Applicant argues that the Walsh reference only teaches one embodiment of the present invention, and does not disclose the countless other embodiments encompassed by the claim. It is

not necessary for a prior art reference to teach all possible embodiments of a claim as long as all of the claim limitations are met by the reference.

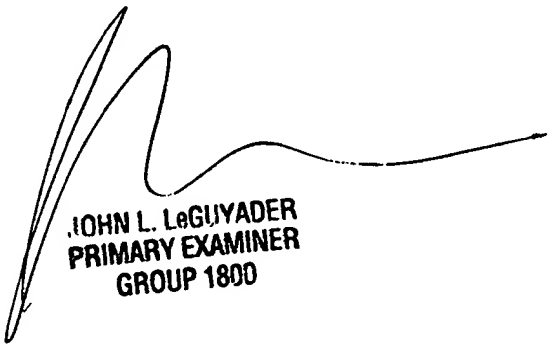
Applicant argues that the rejection of claims 33-35 should be withdrawn because those claims should be entitled to an effective filing date of June 3, 1992 and hence the reference postdates the effective filing date. As discussed *supra*, applicant has not pointed to support in any of the parent applications for the embodiment of claims 33-35, and hence the rejection of claims 33-35 would be applied, if applicant were to amend the claims to delete "therapeutic."

Finally applicant argues that the Walsh reference does not suggest modification of the recombinant adeno-associated vector to include other hypersensitive sites, nor does it suggest modification of the vector to substitute a gene encoding wild-type Factor IX protein, and therefore a rejection under 35 U.S.C. §103(a) is not proper. Although the Walsh reference does not suggest such modifications, it would be obvious to one of ordinary skill in the art to modify the recombinant adeno-associated vectors taught by Walsh to include additional HS sites for it would be expected that additional HS sites would result in enhanced promoter activity. Furthermore, it would be obvious to one of ordinary skill in the art to substitute a gene for Factor IX protein for the globin gene, because substitution of genes on vectors is well known in the art, and particularly since the the teachings of Walsh are directed toward treatment of blood disorders, and Factor IX would be useful for treatment of another blood disorder, hemophelia B. Therefore, if applicant were to amend the claims to delete the term "therapeutic" the rejection under 35 U.S.C. 103(a) would be reinstituted.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy J. Nelson whose telephone number is (703) 306-3218. The examiner can normally be reached on Monday-Friday from 8:00 AM -4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Amy J. Nelson

May 19, 1997